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(54) **REMEDIES FOR DIABETES**

(57) A remedy for diabetes mellitus characterized in that it contains L-arabinose and sucrose (sugar or sugar-containing food or beverage) as effective ingredients. A food or beverage for improvement of diabetes mellitus characterized in that it contains L-arabinose and sucrose (sugar or sugar-containing food or beverage) as

effective ingredients. A method for using L-arabinose characterized in that, for the treatment of diabetes mellitus, L-arabinose is taken together with or prior to ingestion of sucrose (sugar or sugar-containing food or beverage).

**EP 1 340 504 A1**

**Description****Background of the Invention****1. Field of the Invention**

**[0001]** The present invention relates to remedy for diabetes mellitus in which interaction of L-arabinose with sucrose is utilized, to food or beverage for improvement of diabetes mellitus and also to use of L-arabinose for the treatment of diabetes mellitus.

**2. Description of the Related Art**

**[0002]** Although the great part of saccharides in food is starch, a lot of sucrose is taken as the most preferable sweetener throughout the world. In 1996 for example, 87 g and 185g of sucrose/person/day were consumed in Japan and in the United States, respectively. Ingestion of much sucrose tends to induce hyperglycemia and obesity.

**[0003]** Obesity is a well-known dangerous factor for non-insulin-dependent diabetes mellitus (NIDDM). Many of diabetics are persons suffering from NIDDM. In addition to administration of insulin or administration of an SU agent which accelerates the secretion of insulin, administration of an inhibitor of  $\alpha$ -glucosidase, etc. is available for the therapy of NIDDM. The former two agents promote the ingestion of saccharide from blood into cells whereby blood-sugar level is lowered while, in the latter, action of enzyme (glucosidase) which digests and decomposes the saccharide is suppressed and digestion and absorption of the saccharide in small intestine are delayed and/or suppressed to inhibit the ingestion of the saccharide from intestine into blood whereupon a rise in blood-sugar level after meal is suppressed.

**[0004]** On the other hand, L-arabinose has been known to have an action of inhibition of sucrase which is a sucrose-decomposing enzyme in small intestine and it has been recognized that such an action of L-arabinose is utilized to partially inhibit the decomposition of sucrose and to reduce the energy of sucrose. For example, in the Japanese Patent Laid-Open No. Hei-6/65080, there is disclosed that L-arabinose has an action of suppressing the rise of blood-sugar level in mice during 30 to 120 minutes after loading with sucrose. However, that which is disclosed therein is only the above-mentioned action of sucrase-inhibiting of L-arabinose, action of suppression of increase in blood-sugar level after meal and action of suppression of body weight increase caused thereby and, with regard to efficacy of improvement and treatment of diabetes mellitus by lowering the blood-sugar level, it is not made clear.

**[0005]** The present invention has been invented in view of the current state of the prior art as such and its object is to provide a remedy for diabetes mellitus effective to diabetic patient utilizing L-arabinose which results in hypoglycemic action, food or beverage for improvement of diabetes mellitus and method for using L-arabinose for the therapy of diabetes mellitus.

**[0006]** In order to achieve such an object, the present inventors have carried out various studies and, as a result, they have unexpectedly found that, although the sole use of L-arabinose shows only a transient suppressive action to hypoglycemia due to its sucrase-inhibiting action, blood-sugar level of mice is drastically lowered and diabetes mellitus is improved and cured when feed in which L-arabinose is mixed in a specific rate with sucrose which is a causing substance for diabetes mellitus is continuously administered to mice KK-A $\gamma$  which is a model for non-insulin-dependent diabetes mellitus whereupon the present invention has been achieved.

**Summary of the Invention**

**[0007]** Thus, the present invention relates to a remedy for diabetes mellitus which is characterized in containing L-arabinose and sucrose (for example, sugar or sugar-containing food or beverage is used as a source for sucrose) as effective ingredients.

**[0008]** The present invention further relates to food or beverage for improvement of diabetes mellitus which is characterized in containing L-arabinose and sucrose (for example, sugar or sugar-containing food or beverage is used as a source for sucrose) as effective ingredients.

**[0009]** The present invention still further relates to a method for using L-arabinose which is characterized in that, for the treatment of diabetes mellitus, L-arabinose is taken together with or prior to ingestion of sucrose (for example, sugar or sugar-containing food or beverage is used as a source for sucrose).

**Brief Description of the Drawings**

**[0010]**

Fig. 1 shows the changes in blood-sugar level (mg/dl) during the raising period of group A and group B for 30 days.

Fig. 2 shows the changes in blood-sugar level (mg/dl) during the raising period of group C and group D for 30 days.

#### Detailed Description of the Preferred Embodiments

5 [0011] Remedy for diabetes mellitus and food or beverage for the improvement of diabetes mellitus according to the present invention will be specifically illustrated hereinafter although the present invention is not limited thereto.

[0012] With regard to L-arabinose used in the present invention, that which is manufactured by various known methods can be used. For example, there may be used that which is manufactured in high purity and in high efficiency where plant fiber containing L-arabinose as a part of the constituting saccharides is contacted to an acid of low concentration to subject to an acid hydrolysis whereupon L-arabinose is selectively produced as disclosed, for example, 10 in the Japanese Patent Laid-Open No. Hei-11/313700.

[0013] With regard to sucrose used in the present invention, there may be used chemically purified sucrose as well as sucrose-containing substance as a source for sucrose such as sugar or sugar-containing food or beverage. There are various sugar products depending upon material, manufacturing method, degree of purification, color, processed form, etc. thereof and any of them may be used in the present invention so far as it contains sucrose. 15

[0014] With regard to the remedy for diabetes mellitus and the food or beverage for improvement of diabetes mellitus according to the present invention, L-arabinose and sucrose maybe ingested separately with time intervals provided that it is possible to result in a state where L-arabinose and sucrose simultaneously are present in intestine. However, since L-arabinose is slowly absorbed from intestinal tract and remains for long time in intestine while sucrose shows quick digestion and absorption, it is effective for the therapy or the improvement of diabetes mellitus that L-arabinose is ingested together with or prior to ingestion of sucrose (sugar or sugar-containing food or beverage). In the remedy for diabetes mellitus or the food or beverage for improvement of diabetes mellitus according to the present invention, it is preferred that L-arabinose is present in a ratio of 0.5~90% by weight or, preferably, 1~50% by weight to sucrose. When the used amount of L-arabinose is less than the above lower limit, it is not preferred because the effect by the joint use of L-arabinose with sucrose is hardly expressed while, when it is more than the above upper limit, it is not preferred in view of economy since an effect due to its amount cannot be expected. 25

[0015] In addition to the use of L-arabinose and sucrose only, the remedy for diabetes mellitus according to the present invention may also be easily manufactured by combining them with known pharmaceutical carriers to give pharmaceutical preparations. Manufacture of such pharmaceutical preparations is usually conducted in such a manner that L-arabinose and sucrose are compounded with pharmaceutically acceptable liquid or solid carrier and, if necessary, solvent, dispersing agent, emulsifier, buffer, stabilizer, filler, binder, disintegrating agent, lubricant, etc. are added thereto to give solid preparations such as tablets, granules, diluted powder, powder and capsules or liquid preparations such as normal liquid, suspension and emulsion. It is also possible to prepare a dried preparation which can be made into liquid by addition of appropriate carrier thereto before use. 30

[0016] It is preferred that the remedy for diabetes mellitus according to the present invention is an oral preparation so as to effectively express the effect by the joint use of L-arabinose and sucrose. With regard to a pharmaceutical carrier for the oral preparation, there may be used, for example, starch, lactose, white sugar, mannitol, carboxymethylcellulose, corn starch and inorganic salt. For the manufacture of the oral preparation, it is also possible to further compound binder, disintegrating agent, surface-active agent, lubricant, fluidity promoter, corrigent, coloring agent, perfume, etc. therewith. 40

[0017] Dose of the remedy for diabetes mellitus according to the present invention may be appropriately determined depending upon dosage form, administering method, object of use and age, body weight and symptom of the patient applied therewith and, although it is not definite, the amount of L-arabinose contained in the preparation is usually from 1 mg to 10 g/kg per day for adults. It goes without saying that the dose varies depending upon various conditions and, in some cases, less dose than above may be sufficient while, in some other cases, more dose than the above range may be necessary. The remedy for diabetes mellitus according to the present invention maybe daily ingested by adding to any food or beverage as well as oral administration. 45

[0018] Although there is no particular limitation for the manufacturing method of the food or beverage for improvement of diabetes mellitus according to the present invention, there may be exemplified the manufacture by means of cooking, processing and commonly used manufacturing method for food or beverage provided that the manufactured food or beverage contains L-arabinose and sucrose having an improving action for diabetes mellitus as an effective ingredient. With regard to the food or beverage for improvement of diabetes mellitus according to the present invention, there is no particular limitation for its form so far as sucrose and L-arabinose having an improving action for diabetes mellitus are contained therein, added thereto and/or diluted therein and it covers orally applicable forms such as tablets, granules, capsules, gel and sol. 50

[0019] Although the reason why the joint use of L-arabinose and sucrose in the remedy for diabetes mellitus and the food or beverage for improving diabetes mellitus according to the present invention is effective for treatment and improvement of diabetes mellitus has not been clearly elucidated, it is judged that numbers of specific enterobacteria are 55

increased or activated due to the presence of L-arabinose and sucrose at the same time in intestine and that those bacteria produce a substance which is effective for reducing sugar-blood level by promoting the incorporation of saccharide from blood into cells.

## 5 Examples

**[0020]** Effect of the joint use of L-arabinose and sucrose used in the present invention for the therapy or improvement of diabetes mellitus will be illustrated as hereunder.

## 10 Example 1

**[0021]** Twenty model mice for non-insulin-dependent diabetes mellitus showing hyperglycemia (260~270 mg/liter) (KK-A<sup>y</sup>, male, 8 weeks age, Nippon Clair) were preliminarily raised for one week, divided into two groups (group A and group B) and used for the test. Each of the mice was placed in a plastic cage separately and raised by keeping at 23 ± 1°C under a 12-hour bright-and-dark cycle (bright environment from 7 a.m. to 7 p.m. and dark environment from 7 p.m. to 7 a.m. of the next day) where feed and water were freely taken by the mice. Blood-sugar level (concentration of glucose in blood) was measured by a glucose oxidase method after collecting the blood from venous plexus of the eyeground at 9 a.m.

**[0022]** The feed A mentioned in Table 1 (a feed containing α-corn starch, sucrose and cellulose as carbohydrate sources but containing no L-arabinose) was given to the mice of group A while the feed B mentioned in Table 1 (a feed containing α-corn starch, sucrose and cellulose as carbohydrate sources and also containing L-arabinose) was given to the mice of group B and raising was carried out for 30 days.

Table 1

Composition of the Feed				
Composition (% by weight)	Feed			
	A	B	C	D
α-Corn starch	35.85	35.85	55.85	55.85
Sucrose	20	20	0	0
L-Arabinose *1	0	2.5	0	2.5
Cellulose	5.0	2.5	5.0	2.5
Corn oil	6	6	6	6
Mixture of minerals*2	6	6	6	6
Mixture of vitamins *2	2	2	2	2
Choline chloride	0.15	0.15	0.15	0.15
Casein	25	25	25	25

\*1: L-Arabinose (purity: 98%) manufactured by Sanwa Dempun Kogyo K. K.

\*2: manufactured by Oriental Yeast K. K.

**[0023]** Changes in blood-sugar level (mg/dl) of the groups A and B raised as such for a raising period of 30 days are shown in Fig. 1. As will be apparent from Fig. 1, in the group A where there was given the feed A containing sucrose but containing no L-arabinose, blood-sugar level continued in increasing from the 7th day while, in the group B where there was given the feed B containing sucrose and also containing L-arabinose, lower blood-sugar level than the group A was continuously noted from the 7th day, lower blood-sugar level than that at the start of the experiment was noted after the 21st day and, from the 25th day until 30th day, a continuous decrease in the sugar-blood level was apparently noted whereupon an effect of improving and treating diabetes mellitus was expressed.

**[0024]** Result of Example 1 shows an effect of improving and treating the blood-sugar level is expressed as the joint action by simultaneous administration of sucrose and L-arabinose but, only by way of Example 1, there is still a possibility that addition of L-arabinose only may have the same effect. In order to make the possibility clear, an experiment was carried out in the following Reference Example 1 where no sucrose was added to the feed but α-corn starch was added instead of sucrose.

## Reference Example 1

[0025] As same as in Example 1, a feed C mentioned in Table 1 (containing  $\alpha$ -corn starch and cellulose as carbohydrate sources but containing neither sucrose nor L-arabinose) was given to the mice of group C while, to the mice of group D, a feed D mentioned in Table 1 (containing  $\alpha$ -corn starch and cellulose as carbohydrate sources and also containing L-arabinose but containing no sucrose) was given and raising was carried out for 30 days.

[0026] Changes in blood-sugar level (mg/dl) of the groups C and D raised as such for 30 days are shown in Fig. 2. As will be apparent from Fig. 2, mice of both groups C and D continued in increasing the blood-sugar level as same as in the case of the group A of Example 1 during a period of the experiment whereby no improving effect for blood-sugar level was noted. That shows no decrease in blood-sugar level takes place even when only L-arabinose was given without addition of sucrose. Now, results of Example 1 and Reference Example 1 show that high blood-sugar level in model mice for non-insulin-independent diabetes mellitus can be continuously lowered and improved by a simultaneous ingestion of a mixture of sucrose and L-arabinose whereby that is effective for remedy for diabetes mellitus.

[0027] Incidentally, it is not always necessary that sucrose and L-arabinose are administered as a mixture thereof but, for example, with regard to sucrose, food or beverage containing sucrose may be ingested separately. In that case, L-arabinose may be ingested either before or after sucrose although the early ingestion is effective.

## Advantage of the Invention

[0028] In accordance with the present invention, a continuous decrease in blood-sugar level can be achieved by a joint use of sucrose and L-arabinose and that is very useful as a remedy for diabetes mellitus and as food or beverage for improvement of diabetes mellitus.

## Claims

1. A remedy for diabetes mellitus **characterized in that** it contains L-arabinose and sucrose as effective ingredients.
2. The remedy for diabetes mellitus according to claim 1 **characterized in that** it is an oral preparation.
3. The remedy for diabetes mellitus according to claim 1 **characterized in that** sugar or sugar-containing food or beverage is used as a source for sucrose.
4. The remedy for diabetes mellitus according to any one of claims 1~3 **characterized in that** L-arabinose is present in a ratio of 0.5~90% by weight to sucrose.
5. A food or beverage for improvement of diabetes mellitus **characterized in that** it contains L-arabinose and sucrose.
6. The food or beverage for improvement of diabetes mellitus according to claim 5 **characterized in that** L-arabinose is present in a ratio of 0.5~90% by weight to sucrose.
7. A method for using L-arabinose **characterized in that**, for the therapy of diabetes mellitus, L-arabinose is taken together with or prior to ingestion of sucrose.
8. The method for using L-arabinose according to claim 6 **characterized in that** sugar or sugar-containing food or beverage is used as a source for sucrose.

Fig. 1

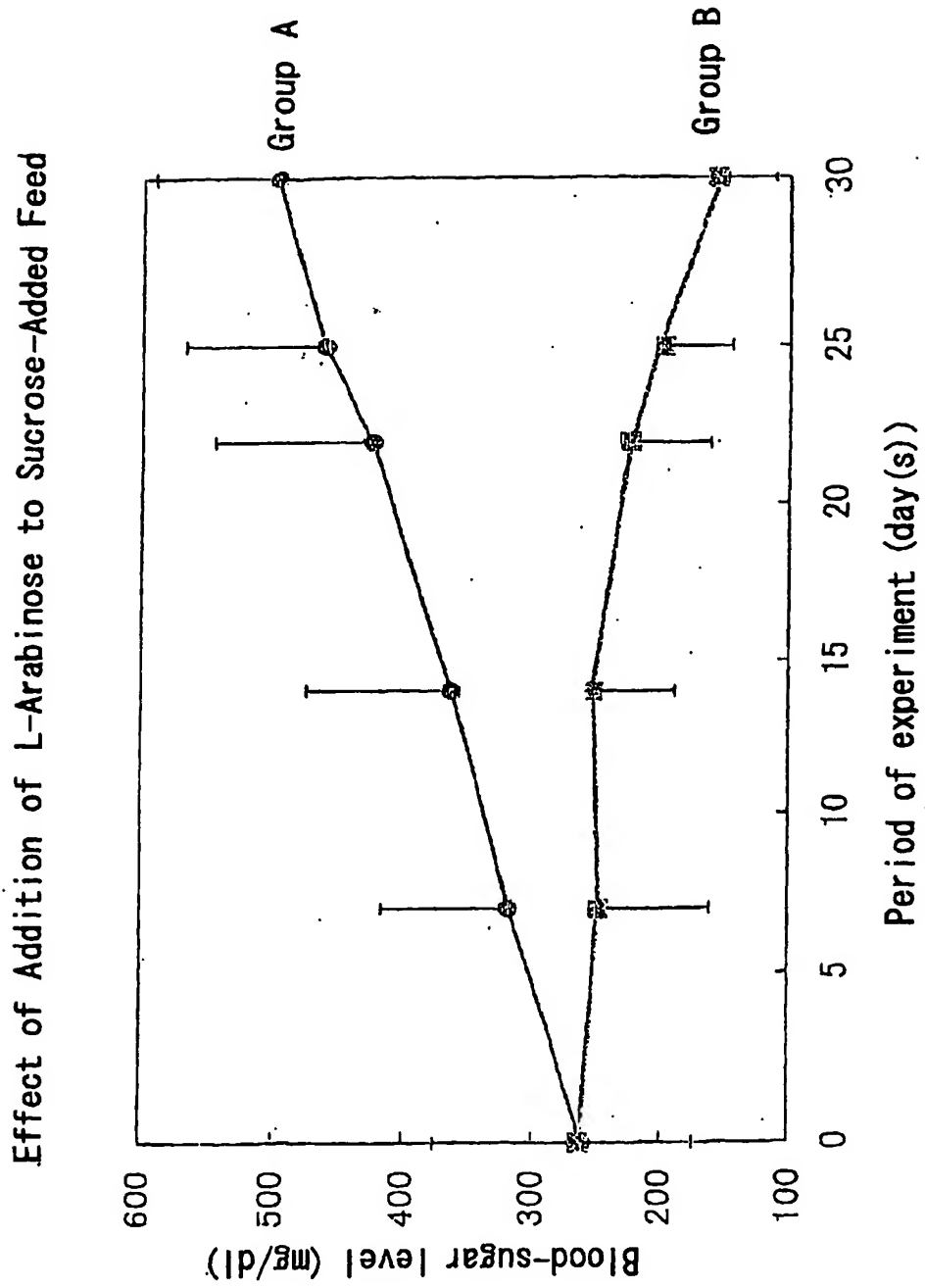
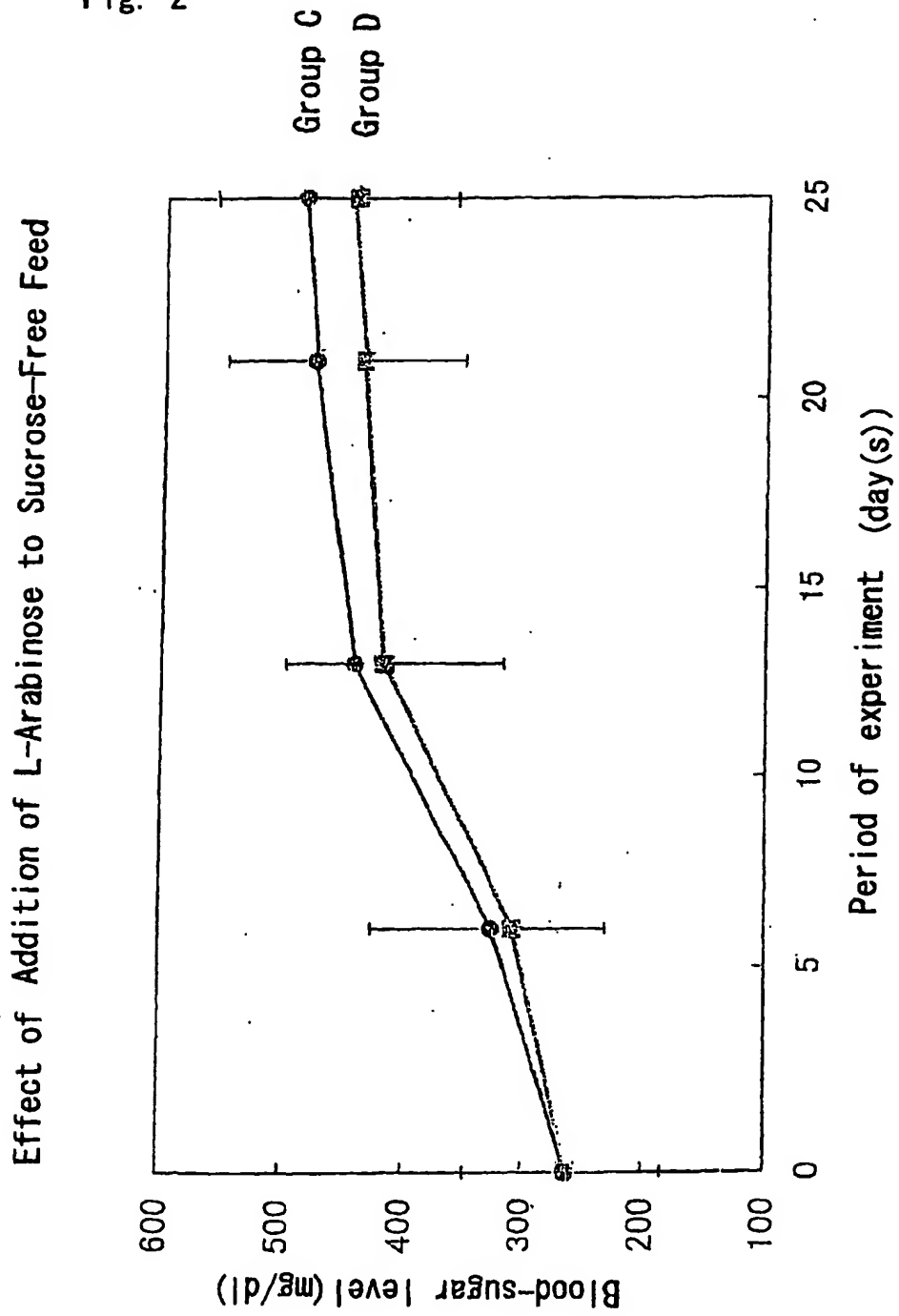


Fig. 2



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/09542

A. CLASSIFICATION OF SUBJECT MATTER Int.Cl. <sup>7</sup> A61K31/7004, 7016, A23L1/30, 2/00, A61P3/10		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.Cl. <sup>7</sup> A61K31/7004, 7016, A23L1/30, 2/00, A61P3/10		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS, REGISTRY (SYN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 8-23973 A (Hokuren), 30 January, 1996 (30.01.96) (Family: none)	1-6
X	EP 560284 A1 (Gogo Shusei Co., Ltd.), 15 September, 1993 (15.09.93), & JP 6-65080 A & CA 2091049 A & US 5468734 A	1-6
X	WO 94/12057 A1 (Fujisawa Pharm. Co., Ltd.), 12 November, 1994 (12.11.94) (Family: none)	1-6
PX	Nippon Eiyo Shokuryo Gakkaishi, (2001), 54(3), pages 155 to 160	1-6
PX	Nippon Eiyo Shokuryo Gakkaishi, (2000), 53(6), pages 243 to 247	1-6
X	J. Appl. Glycosci., (1999), 46(2), pages 159 to 65	1-6
X	Kagaku to Seibutsu, (1997), 35(12), pages 824 to 826	1-6
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>		
Date of the actual completion of the international search 10 December, 2001 (10.12.01)		Date of mailing of the international search report 18 December, 2001 (18.12.01)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
Facsimile No.		Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/09542

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(e) for the following reasons:

1. ☒ Claims Nos.: 7,8  
because they relate to subject matter not required to be searched by this Authority, namely:

The inventions as set forth in claims 7 and 8 pertain to methods for treatment of the human body by therapy.

2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)